REMARKS

This Reply is submitted in response to the Office Action dated June 13, 2000. Reconsideration and re-examination pursuant to 37 C.F.R. §1.112 are respectfully requested.

First, new claims 7-14 are submitted above. Claim 7 emphasizes one embodiment of the invention, wherein a patient undergoing treatment for a B cell lymphoma or leukemia is treated with an antibody specific for a B cell antigen after transplantation of bone marrow or peripheral stem cells in order to purge contaminating B cells that may have been introduced via the transplantation. Support for claim 7 may be found in original claim 1, which, like new claims 8-9, also encompasses in vitro purging of bone marrow and peripheral stem cells harvested prior to aggressive therapy. New claim 7 also emphasizes that the in vivo and in vitro purging of the present invention is particularly effective where the patient had undergone one or more prior high dose (aggressive) therapies selected from the group consisting of radioimmunotherapy, whole body irradiation, chemotherapy, cytokine treatment and antibody therapy, wherein said antibody binds to an antigen expressed on the surface of malignant B cells. Support for this limitation may be found in the specification at the very least at page 3, line 14, page 6, second full paragraph, and the paragraph bridging page 11.

New claims 8 and 9, besides finding support in original claim 1, are also supported in the specification at page 6, paragraphs 1-3. New claim 10 recites a preferred embodiment of the invention, wherein the prior high dose therapy is RITUXAN and/or radioimmunotherapy. Support for this claim may be found in the last paragraph of page 5. New claims 11-12 specify that the purging agent may be either an anti-CD19 or anti-CD20 antibody or fragments thereof, and that the antibody may be chimeric, primate, primatized, humanized or human. Support for this claim may be found on page 7, third paragraph. Most preferably, as

recited in new claim 13, the purging agent is RITUXAN, although purging may be accomplished with other therapeutic anti-CD20 and anti-CD19 antibodies, as well as other antibodies that bind to antigens on the surface of malignant B cells, and by binding effect purging or depletion. This claim finds support throughout the specification, particularly at the last line of page 4. Finally, new claim 14 refers to an acceptable dose range and administration scheme for RITUXAN after transplant, and finds support in original claim 4 and in the specification at page 6, last paragraph. No new matter has been added.

Turning now to the Office Action, claims 1-6 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Anderson et al, U.S. Patent 5,736,137 (the '137 patent). Essentially, it is the Examiner's position that the '137 patent teaches the combined administration of chimeric and radiolabeled anti-CD20 antibodies, and that such treatment may be followed by administration of previously collected and purged autologous bone marrow cells (in reference to col. 10 of the patent). The Examiner acknowledges that the '137 patent does not teach the preamble of claim 1, i.e., a method for reducing the risk of relapse, and that the '137 patent does not teach in vitro purging. However, the Examiner also believes that these elements would have been obvious to the routineer based on the teaching in the '137 patent that anti-CD20 could be used to effectively remove CD20+ cells (in reference to col. 8, which mentions that anti-CD20 antibodies can be used to deplete B cells from bone marrow). Applicants respectfully traverse the rejection as it applies to original claims 1-6 and request that the rejection as to the original claims be withdrawn. Further, Applicants respectfully submit that the rejection is also not applicable to new claims 7-14.

First, Applicants respectfully reiterate that original claims 1-6 deal especially with the problem of relapse of patients having B cell lymphomas and leukemias. Because the '137

patent did not deal with the problem of relapse of patients following initial therapy, it could not have rendered obvious the utility that anti-CD20 and other antibodies to B cell antigens would have in effecting treatment in patients that have relapsed after other therapies. Furthermore, the general reference in the '137 patent with regard to combination therapies of radiolabeled anti-CD20 and unlabeled anti-CD20 would not render obvious the unexpected efficacy demonstrated by administering antibodies to B cell surface antigens following high dose therapy and transplantation of bone marrow or peripheral blood stem cells. New claim 7 in particular emphasizes this novel treatment method wherein an antibody to a malignant B cell surface antigen is administered after transplantation of bone marrow or peripheral stem cells in order to purge cells present in the transplant.

As noted in the Office Action, the '137 patent does mention that bone marrow or peripheral stem cells can be harvested and frozen for *possible* reinfusion. However, in contrast to the methods of the present invention, the '137 patent makes this suggestion as merely a preventative measure designed to reconstitute the blood cells just in case there is unacceptable marrow toxicity. In fact, the '137 patent prefers that diagnostic dosimetry be used to protect against yttrium toxicity, thereby foregoing the need to reinfuse bone marrow cells (see col. 10, lines 8-21). And even supposing that there was unacceptable marrow toxicity following treatment with the radiolabeled antibody in the '137 patent, the '137 patent does not suggest that patients should undergo further anti-CD20 antibody treatments after reinfusion of bone marrow cells. Most importantly, the '137 patent does not disclose the unexpected efficacy that is achieved when antibodies to antigens on the surface of malignant B cells are administered after high dose therapies combined with transplantation of bone marrow and peripheral stem cells.

The fact that the harvesting and subsequent reinfusion of the bone marrow cells in the '137 patent is disclosed merely as a preventative measure is further evidenced by the protocol at col. 19, lines 41-49, of the '137 patent. This protocol is outlined as follows:

1. Peripheral stem cell (PSC) or bone marrow (BM) harvest with purging;
2. I2B8 (indium labeled anti-CD20 antibody) imaging;
3. Y2B8 (yttrium labeled anti-CD20 antibody) therapy;
4. PSC or autologous BM transplantation (if necessary based upon absolute neutrophil count below 500/mm_3 for three consecutive days or platelets below 20,000/ mm_3 with no evidence of marrow recovery on bone marrow examination). (With emphasis).

There is absolutely no mention in this protocol that the cells which are reinfused might be contaminated with tumor cells; there is absolutely no suggestion that the patient should or would benefit by treatment with unlabeled anti-CD20 antibody subsequent to reinfusion; and there is certainly no disclosure that treatment with anti-CD20 antibodies subsequent to bone marrow or peripheral stem cell transplant reduces the risk of relapse and improves the response rate over protocols including BM or PSC reinfusion without subsequent purging.

The advantages of the treatment methods of the claimed invention are illustrated in the results reported at the bottom of page 11 of the instant specification. Significantly, in 23 patients who relapsed after BM or PBSC transplantation, the over-all response rate was 78% versus 43% in patients who had not undergone prior high dose therapy plus transplantation ($p<0.01$). This suggests that a combined treatment protocol including high dose therapy plus BM or PBSC transplantation followed by purging with anti-CD20 antibody provides a beneficial and synergistic effect over either single treatment alone.

The Federal Circuit has acknowledged that one way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of "unexpected results," i.e., to show that the claimed invention exhibits some superior property or advantage that a person of

ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward- that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results. In re Soni, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995).

It is the Examiner's opinion that one of ordinary skill in the art would have routinely performed the combination treatment protocols of the claimed methods based on the teachings of the '137 patent alone. Combined with the observation that the '137 patent did not suggest to follow up BM/PSC reinfusion with administration of anti-CD20 antibody, the fact that such subsequent administration has such a significant beneficial effect on response rate and the risk of relapse is particularly persuasive evidence that should be sufficient to rebut a *prima facie* case of obviousness based on the '137 patent.

Also persuasive is the number of reports in the literature that have been published since the '137 patent was issued (and after the priority date of the present application) which herald the benefits of administering anti-CD20 antibody after high dose therapy plus BM/PSC transplantation for the treatments of various B cell lymphomas and leukemias. For instance, Rottenburger et al. (Br. J. Haematol. 1999) speculate that peripheral CD19+ and CD20+ B cells persist after conventional high dose therapy and PBSC transplant, and could be a source of relapse for patients with multiple myeloma. The authors report that anti-CD20 antibody treatment could be a "promising" approach for the eradication of malignant cells in the peripheral blood of patients even in continuous remission after high dose therapy and PBSC transplant. Similarly, Kiel et al. (Bone Marrow Transplant 1999) report that CD19+

cells persist after high dose therapy, and that these cells contribute to disease dissemination and relapse. Buckstein et al. (Semin. Oncol. 1999) disclose a "pivotal" clinical trial revealing that response rates to rituximab (same as RITUXAN) were higher in patients who previously had high dose therapy and autologous stem cell transplantation. Magni et al. (Blood 2000) disclose an in vivo purging method using rituximab which they claim is capable of providing tumor-free stem cell products from most patients with mantle cell or follicular lymphoma and bone marrow involvement, which resulted in a "more-than-additive" antilymphoma effect with regard to complete response rate. Tarella et al. (Leukemia 1999) reported that ex vivo purging combined with high dose chemotherapy and PBSC autograft results in long-term clinical remission in non-Hodgkin's lymphoma patients, and particular those patients with follicular lymphoma. And Tsai et al. (Bone Marrow Transplant. 1999) report that rituximab has "significant activity" in the treatment of intermediate-grade non-Hodgkin's lymphoma in patients that had relapsed after PSC transplantation. Copies of these references are attached for the Examiner's convenience.

The observations made in the above references concerning the persistence of CD19+ and CD20+ cells in the blood of patients previously treated with high dose therapies, and the "promising," "pivotal," "more-than-additive" and "significant" results obtained with anti-CD20 antibodies in treating various relapsed lymphoma patients, suggests that neither the persistence of cells after high dose therapy, nor the reported combination therapy was obvious to these researchers. In particular, the approach of treating lymphoma patients with anti-CD20 antibody after high dose therapy plus PBSC transplantation was not obvious to these researchers even after the '137 patent had issued.

As set forth in Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 7 USPQ2d 1222 (Fed. Cir. 1988), a *prima facie* showing of obviousness may be rebutted with evidence of commercial success, when there is a nexus established between the merits of the claimed invention and the evidence offered. A *prima facie* case of nexus is generally made out when the [applicants] show both that there is commercial success and that the thing that is commercially successful is the invention disclosed and claimed. See Ex parte Remark, 15 USPQ2d 1498, 1503 (PBAI 1990). Applicants respectfully submit that the fact that at least four of the groups of researchers which authored the above-referenced articles used applicants' preferred purging agent (RITUXAN), in a subsequent administration after high dose therapy plus PBSC transplant, and further given that each of these group reported a significant level of success, provides a sufficient nexus between applicants' claimed invention and the commercial success to be gleaned from the claimed method.

In summary, the '137 patent fails to disclose or even suggest the administration of anti-CD20 or any other antibody subsequent to the reinfusion of bone marrow or stem cells. Further, the '137 patent only suggests the harvesting of bone marrow as a preventative measure to be practised in addition to dosimetry and low dose therapy, to avoid fatal bone marrow toxicity associated with radioimmunotherapy. The '137 patent certainly does not render obvious the unexpected beneficial results to be gained with regard to relapse and response rate by combining high dose therapy, BM/PBSC transplant and subsequent anti-CD20 therapy. Moreover, given that several researchers have heralded the surprising advantages to be gained in the treatment of a wide variety of B cell malignancies using applicants' claimed method suggests there is a nexus between the commercial success of the approach and the claimed invention sufficient to rebut a *prima facie* case of obviousness.

Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) in view of all of the above is respectfully requested.

This Reply is believed to be fully responsive to the Office Action dated June 13, 2000. Therefore, a Notice of Allowance appears to be next in order. If the Examiner should have any questions relating to this Reply or the application in general, he is respectfully requested to telephone the undersigned so that prosecution may be expedited.

Respectfully submitted,

SHAW PITTMAN

By: _____
Bonnie D. Weiss
Registration No. 43,255

2300 N. Street, NW
Washington, DC 20037-1128
(202) 663-8000

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